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TITLE: The Epidemiology of Epilepsy and Traumatic Brain Injury: Severity, Mechanism, and Outcomes

PRINCIPAL INVESTIGATOR: Mary Jo Pugh, PhD RN

CONTRACTING ORGANIZATION: Foundation for Advancing Veterans Health Research
San Antonio, TX 78229

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Mary Jo Pugh

E-Mail: pughm@uthscsa.edu

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Foundation for Advancing
Veterans Health Research
7400 Merton Minter Blvd
San Antonio, TX 78230-4404

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14. ABSTRACT

Our previous research has found that Post-9/11 Veterans with any kind of traumatic brain injury (TBI) were more likely to develop epilepsy than those without a prior TBI – however, its association with closed head injury such as mild TBI is as of yet unclear. To begin to rigorously evaluate this association, we have reviewed the 7238 cases of epilepsy identified using International Classification of Diseases Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis codes in Department of Veterans Affairs care, finding that 4664 (64.4%) were valid cases of epilepsy. We hope to use the results of this research to identify risk factors for post-traumatic epilepsy that will enable early identification for those at risk of its development.

15. SUBJECT TERMS
Epilepsy, diagnoses, verification

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1. **INTRODUCTION**

Studies of Veterans from World War II, the Korean War, and Vietnam provided groundbreaking information regarding the understanding of combat-related traumatic brain injury (TBI) and epilepsy. Because these studies focused on penetrating TBI (pTBI), our understanding of the association of closed head injuries including mild TBI (mTBI)—the majority of TBI exposures—with posttraumatic epilepsy (PTE) is unclear. By conducting an expansive evaluation of epilepsy epidemiology in Post-9/11 Veterans deployed in support of Wars in Iraq and Afghanistan using available data from the Departments of Defense (DoD) and Veterans Affairs (VA) and primary data collection allows us to go beyond a simple incidence/prevalence study to provide a targeted evaluation of the impact of epilepsy on Post-9/11 Veterans compared to controls, and to harness the power of cutting-edge neuroimaging (and eventually biomarker) data to answer immediate questions regarding etiology and provide the foundation for longitudinal study that will ultimately identify specific aspects of mTBI/other risk factors that will allow early identification of those at greatest risk of PTE.

2. **KEYWORDS:**

Epilepsy, mild traumatic brain injury, epidemiology

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**
  - Major Task 1: Complete Regulatory Requirements for Study
  - Major Task 2: Identify cohort who meet criteria for epilepsy (Aim 1)
  - Major Task 3: Identify Sample for Aims 2-3
  - Major Task 4: Conduct telephone interviews/surveys for Veterans with Epilepsy and Controls to conduct analyses for Aims 2 and 3
  - Major Task 5: Identify TBI phenotypes
  - Major Task 6: Conduct analyses comparing Veterans with epilepsy and controls on self-report measures (Aim 3)
  - Major Task 7: Conduct analyses comparing Veterans with epilepsy and controls on neuroimaging and neuropsychological testing (Aim 4)

- **What was accomplished under these goals?**

  - **Major Task 1: Complete Regulatory Requirements for Study**
    We have finalized consent forms, human subjects protocols, and the chart abstraction tool, survey, and interview needed to conduct all work outlined in this grant. Further, we have secured local regulatory (Department of Veterans Affairs (VA) Research and Development and Institution Review Board) approval at all sites (i.e., South Texas Veterans Healthcare System (Site 1), University of Missouri, St. Louis (UMSL; Site 2), Hunter Holmes McGuire VA Medical Center (Richmond, VA; Site 3), Tampa VA Research and Education Foundation (TVREF; Site 4); Baylor University (BU; Site 5), as well as at the additional Chronic Effects of Neurotrauma Consortium (CENC) Longitudinal Cohort Study (Study 1) sites of Portland, OR and Boston, MA. We have received Human Rights Protection Office approval for Aims 1-3 (Research Activities local to the main site in San Antonio, TX), but await final approval for all additional sites (Aim 4); despite this delay, in part due to a change in HRPO specialist during the review process, there is no delay currently anticipated regarding the outlined statement of work, as Aim 4 work is not set to commence until mid-to-late calendar year 2018.
  - **Major Task 2: Identify cohort who meet criteria for epilepsy (Aim 1)**
    We have secured VA all proposed VA data and have completed medical chart reviews to validate diagnoses of epilepsy identified based on International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis codes. However, we have not yet had an opportunity to combine VA and Department of Defense (DoD) data because of administrative delays outside of our control with securing HRPO IRB approval and access to DoD data sources. This delay will not impact the progression of our work because it can be done concurrent to our survey efforts.
  - **Major Task 3: Identify Sample for Aims 2-3**

We have completed medical chart reviews to validate the 7238 diagnoses of epilepsy identified based on International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis codes in VA data, therefore the work on this task is complete, well ahead of schedule.

- **Major Task 4: Conduct telephone interviews/surveys for Veterans with Epilepsy and Controls to conduct analyses for Aims 2 and 3**
  We are currently preparing to field a small number (~500) of surveys and interviews in the last quarter of calendar year 2017 (ahead of schedule) to ensure that the larger scale survey effort is executed as smoothly as possible during the scheduled time frame of calendar year 2018.
- **Major Task 5: Identify TBI phenotypes**
  Work on this task will begin in late calendar year 2018/early 2019 once the survey is fielded and a sufficient number of responses have been received.
- **Major Task 6: Conduct analyses comparing Veterans with epilepsy and controls on self-report measures (Aim 3)**
  Work on this task will begin in late calendar year 2019 once the survey is fielded and a sufficient number of responses have been received.
- **Major Task 7: Conduct analyses comparing Veterans with epilepsy and controls on neuroimaging and neuropsychological testing (Aim 4)**
  Once HRPO IRB approval is received for Aim 4 and surveys are returned for which individuals indicate consent to be contacted/recruited into the CENC Longitudinal Cohort Study (Study 1) through which these neuropsychological and neuroimaging measures will be collected, work on this task will commence.

- **What opportunities for training and professional development has the project provided?**
  Nothing to Report.
- **How were the results disseminated to communities of interest?**

  Nothing to Report.
- **What do you plan to do during the next reporting period to accomplish the goals?**

  During the next year, we plan to continue to pursue HRPO IRB approval (Major Task 1), DoD data access (Major Task 2), and execute the survey (Major Tasks 4-7).

4. **IMPACT:**

The chart abstraction process revealed a significant number of individuals who died since meeting epilepsy criteria. We plan to further evaluate the cause of death and the impact of comorbidity phenotypes on mortality in a separate proposal using this study as a foundation.

- **What was the impact on the development of the principal discipline(s) of the project?**

Through the epilepsy verification process we have identified revisions to the algorithm that may make the epilepsy algorithm even more useful for surveillance purposes in both VA and DoD data.

- **What was the impact on other disciplines?**

  Nothing to Report.
- **What was the impact on technology transfer?**

  Nothing to Report.
- **What was the impact on society beyond science and technology?**

  Nothing to Report.

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

  Nothing to Report.

- **Actual or anticipated problems or delays and actions or plans to resolve them**
  - *Delayed HRPO IRB Approval: Because of the complexity of this project, the numerous sites involved in this interdisciplinary work, and a change in the assigned HRPO Specialist assigned to this project, we have been delayed in securing HRPO IRB approval for Aim 4 and the sites involved in that work. We plan to continue working diligently with HRPO to secure that approval.*
  - *Delayed access to DoD data sources: Due in part to the delay in HRPO IRB approval as well as administrative delays both local to the San Antonio study site's institutional regulatory support and the DoD data administrators, access to these data have been delayed. We submitted documentation to secure access to these data sources in May/June 2017 and await further capability to complete and execute these requests. We will continue to work with local administrators and DoD data stewards to gain access to this data as soon as possible.*
- **Changes that had a significant impact on expenditures**

  Delay in data access reduced the amount of time that data analyst was required this Fiscal Year. Thus, increased data analyst cost will be required in future fiscal years as this work is accomplished.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  Nothing to Report.

6. **PRODUCTS:**
   - **Publications, conference papers, and presentations**
   - **Journal publications.**

     Nothing to Report.
   - **Books or other non-periodical, one-time publications.** Nothing to Report.
   - **Other publications, conference papers, and presentations.** Nothing to Report.
- **Website(s) or other Internet site(s)**

  Nothing to Report.

- **Technologies or techniques**

  Nothing to Report.

- **Inventions, patent applications, and/or licenses**

  Nothing to Report.

- **Other Products**

  Nothing to Report.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Name:	*Mary Jo Pugh*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	*Dr. Pugh has overseen project startup planning.*
Funding Support:	

Name:	*Alicia Swan*
Project Role:	*Research Scientist*
Researcher Identifier (e.g. ORCID ID):	*orcid.org/0000-0003-2412-0499*
Nearest person month worked:	12
Contribution to Project:	*Dr. Swan has completed regulatory requirements and project startup planning and execution.*
Funding Support:	

Name:	*Katharine McMillan*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6
Contribution to Project:	*Dr. McMillan has completed the epilepsy diagnosis validations described under Major Task 3.*
Funding Support:	

Name:	*Shaila Gowda*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Dr. Gowda has provided input regarding epilepsy items included on the survey and guided epilepsy case validation.*

Funding Support:	

Name:	*Sunchai Khemalaap*
Project Role:	*Program Manager*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*
Contribution to Project:	*Mr. Khemalaap assisted with developing contracting between primary and secondary sites.*
Funding Support:	

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  Nothing to Report.

- **What other organizations were involved as partners?**

  Nothing to Report.

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:** Not Applicable.
- **QUAD CHARTS:** Attached.

9. **APPENDICES:** None.

The Epidemiology of Epilepsy and Traumatic Brain Injury: Severity, Mechanisms, and Outcomes

ERMS/EP150013

W81XWH-16-2-0046

PI: Mary Jo Pugh PhD, RN **Org:** Foundation for Advancing Veterans Health Research **Award Amount:** $2,199,189

Study Aims

•Aim 1: Identify a cohort of Post-9/11 Veterans who received VA care during at least two years (2002-2015), calculate the prevalence of epilepsy in 2015 and identify the association between mTBI and epilepsy

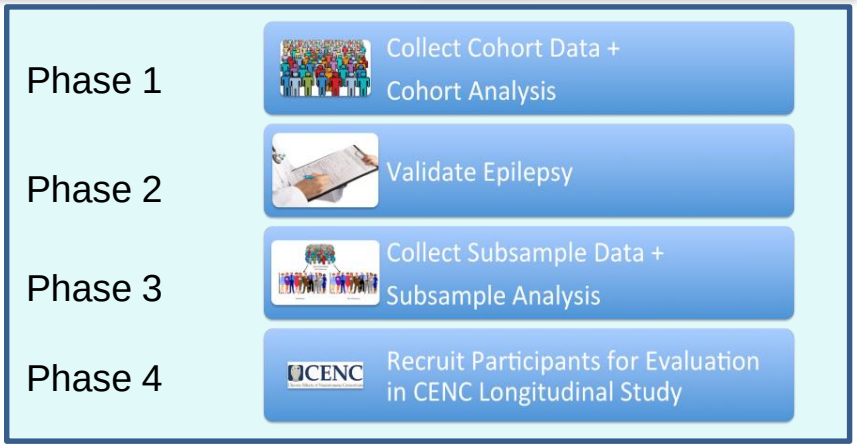
• Aim 2: Among a subsample of surveyed Veterans, examine the association between lifetime history of mTBI and epilepsy.

• Aim 3: Among the surveyed subsample, compare those with and without epilepsy on functional outcome measures (e.g., employment status, mental, physical and social functional status, community reintegration).

• Aim 4: Enroll 200 survey respondents in the Chronic Effects of Neurotrauma Consortium (CENC) Longitudinal study to obtain advanced clinical, cognitive, and MRI data.

Approach

This study utilizes data from existing VA and DoD data repositories, patient self-reports from surveys/interviews and data collected through the CENC longitudinal study. These unique data sources will allow us to examine population prevalence of epilepsy, identify its association of mTBI, assess outcomes associated with epilepsy, and reveal neuroimaging and biomarker correlates of mTBI and epilepsy. The longitudinal nature of the CENC longitudinal study provides an opportunity to follow this cohort beyond the course of this study to better understand the long-term impact of mTBI exposures and epilepsy among the Veterans of the Afghanistan and Iraq wars.



Accomplishments: We have local IRB and R&D approvals for the primary site and HRPO approval for Aims 1-3. All of the CENC Study 1 sites have local approval except Houston, TX. We have approval for all VA data sources and have submitted the DoD data requests. Our team has completed more than 65% of the 7000 epilepsy chart verifications and finalized our survey thanks to our epilepsy subject matter experts. The survey will be deployed starting in FY17 Q4.

Timeline and Cost

Activities / CY	17	18	19	20
Identify Cohort and estimate prevalence of epilepsy				
Examine association between lifetime mTBI and epilepsy				
Compare surveyed Veterans with and without epilepsy on outcomes				
Obtain clinical, cognitive, and MRI data on the select CENC subsample				
Estimated Budget ($K)	**$508**	**$558**	**$568**	**$566**

Updated: October 3, 2017

Goals/Milestones

CY17 Goal – Regulatory approval, data acquisition, survey design

☑ Gain regulatory approval and logistical readiness to execute aims

CY18 Goals – Survey administration, data compiling, aim 1 analysis

☐ Calculate epilepsy prevalence and its association with mTBI

☐ Begin compiling survey data

CY19 Goal – Finalize survey data, chart abstractions, and commence referral to and enrollment in CENC study 1

☐ Execute analyses of outcomes among the surveyed Veterans with and without epilepsy and a history of mTBI

CY20 Goal – Complete enrollment and testing 150-200 of the surveyed subsample in the CENC Longitudinal Cohort study

☐ Analyze advanced clinical, cognitive and MRI data among those referred to CENC study 1

Comments/Challenges/Issues/Concerns

- No challenges, roadblocks or concerns to date

Budget Expenditure to Date

Projected Expenditure: $508,364

Actual Expenditure: $217,482